

DOCKET NO.: BTG0004-100 (141183US01)

PATENT

**REMARKS**

Claims 1-47 were pending in the present application. Claim 4 has been canceled without prejudice to its presentation in another application. Claims 1, 5, 6, 12, 22, 23, and 47 have been amended herein. No new matter has been added. Upon entry of the present amendment, claims 1-3, 5, 6, 12-24, and 47 will be pending.

As a preliminary matter, although Applicants disagree with the reasoning set forth in the Office Action regarding the restriction requirement, Applicants nonetheless affirm the election.

Claims 1, 12, 22 and 47 have been amended to recite that the protein or peptide comprises at least one of a) the DNA binding domain, b) the heterodimerization domain, and c) the nuclear localization signal. Basis for this amendment is found, for example, on page 12, lines 3-7 of the specification.

Claim 1 has been amended to recite the step of "transforming a plant cell with a nucleotide sequence that comprises a sequence encoding a peptide or protein with E2F-dimerization partner (DP) protein activity in a plant cell." Basis for this amendment is found, for example, in the general teaching of the text and particularly on page 12, line 16 of the specification. The phrase "E2F activity" has been defined as "E2F binding to E2F binding sites in plant DNA" which is derived from, for example, line 28 and 29 of page 10 of the specification. The term "alter" has been amended to "modulate" based on, for example, line 28, page 10 of the specification. The phrase "is capable of interacting with" has been amended to recite "dimerizes with." The phrase "in the plant cell" as been added to provide antecedent basis. The term is based on the description at, for example, page 10, line 8.

The subject matter of claim 4 has been incorporated into claim 1.

Regarding claim 5, the term "alter" ..... "DP/E2F binding activity" has been amended to recite "increase or decrease the binding of DP to E2F." This amendment is based on the overall teaching of the text and particularly at lines 15-18, page 9, lines 25-26, and page 10, lines 7-10 of the specification. The phrase "transactivation properties" has been amended to recite "E2F-DP transactivation properties." This amendment is based on the overall teaching of the text and particularly at, for example, page 10, lines 11-13 of the specification. The phrase "altering

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transactivation properties" has been amended to "altering E2F-DP transactivation properties." This further clarifies to which protein's properties are being referred.

Regarding claim 6, the term "may" has been amended to recite "is." The term "DP" has been amended to recite "DP protein activity." The term "modified" has been amended to recite "increased or decreased."

Regarding claim 12, the phrase "for expression of" has been removed. The phrase "capable of altering" has been amended to recite "that increases or decreases"; the phrase "effect thereof" has been removed.

Claim 22 has been amended to recite "a nucleic acid having a DP protein or peptide encoding sequence together with a sequence encoding an E2F protein or peptide," support for which is found in the paragraph spanning pages 15 and 16 of the specification. The phrase "is capable of altering" has been amended to read "increases or decreases" as supported, for example, at line 25 and 26 of page 9 of the specification.

Claim 23 has been amended to recite the regulatory element.

The phrase "is capable of altering" in claim 47 has been amended to recite "increases or decreases" as supported, for example, at line 25 and 26 of page 9 of the specification. The phrase "ability to dimerize" has been amended to "dimerization." The phrase "ability to modulate" has been amended to "modulation of." The phrase "effect thereof" has been removed.

### I. The Claimed Invention Is Useful

Claims 1-6, 12-24 and 47 are rejected under 35 U.S.C. §101 as allegedly failing to be supported by either a specific, substantial, or a well-established utility. The Office Action asserts that Applicants have not established a specific use for the claimed DNA sequences, and thus, the claimed DNA sequences have no real-world use. Applicants traverse the rejection and respectfully request reconsideration thereof because the claims are supported by specific, substantial, and credible utilities.

The protein comprising SEQ ID NO:2 is a previously undescribed member of the E2F dimerization partner proteins. This activity has been established through a combination of sequence similarity and functional evidence as presented in the application, for example, in

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Examples 5, 6 and 7 and Figure 3. In addition, the protein binds to, and modulates the binding to DNA of a plant E2F transcription factor, a protein known to be involved in the transition of G1/S phases in the cell cycle. The description at page 4, line 14 to page 5, line 10 provides specific, substantial, and credible uses for modulation of these activities. Furthermore, these specific, substantial, and credible uses are supported by the teaching of PCT Publication WO0047614 (applicant Pioneer) which discusses even more specific, substantial, and credible uses for plants with modified expression of the DP proteins. Because the protein comprising SEQ ID NO:2 clearly has at least one specific, substantial, and credible utility, the DNA encoding such a protein also has at least one specific, substantial, and credible utility.

Thus, the claimed DNA clearly has a useful, concrete and tangible use and, thus, is patentable subject matter. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §101/§112 be withdrawn.

## **II. The Claimed Invention Is Novel**

Claims 17-20 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Gillaspy et al., GenEmbl Accession No. U39059 (18 November 1996) (hereinafter, the "Gillaspy reference"). The Office Action asserts that the Gillaspy reference reports a DNA sequence consisting of 60 contiguous nucleotides of SEQ ID NO:1 that are not selected from nucleotides encoding amino acids 70 to 136. Applicants traverse the rejection and respectfully request reconsideration because the Gillaspy reference does not teach every feature recited in claims 17-20.

A sequence alignment of the Gillaspy sequence and SEQ ID NO:1 shows only that the two sequences possess 52 contiguous adenosines in common in the poly A tail and 8 other bases in common. The Gillaspy sequence, however, does not represent a nucleic acid probe because it has only limited GC content and does not appear likely to act as a probe at a reasonable stringency; nor would it represent a suitable primer because it does not appear likely to bind to the target at the temperatures normally used for specific amplification. Further, one skilled in the art would be very unlikely to select a probe that contains a sequence that is quite clearly not in

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any way specific to a particular sequence. Thus, although the Gillaspy sequence is a DNA sequence, it does not amount to a probe or primer.

Thus, the Gillaspy reference does not teach every feature recited in claims 17-20. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §102(b) be withdrawn.

### **III. The Claims Are Clear And Definite**

Claims 1, 3-6, 12-16, 22-24, and 47 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as their invention. Although Applicants believe the claims are clear and definite as originally drafted, solely to advance prosecution of the present application, Applicants have amended the claims to be even more clear and definite. No new matter has been added. The claims have not been narrowed.

#### *A. Claim 1*

The Office Action asserts that claim 1 lacks an essential step. Although Applicants disagree, solely to advance prosecution of the present application, Applicants have amended claim 1 to recite the step of "transforming a plant cell with a nucleotide sequence that comprises a sequence encoding a peptide or protein with E2F-dimerization partner (DP) protein activity in a plant cell."

The Office Action also asserts that claim 1 is indefinite in recitation of "controlling." Claim 1 recites a "method of controlling one or more of plant growth, gene expression, cellular DNA replication, cell cycle progression, differentiation and development..." The Office Action asserts that it is unclear "how" plant growth, gene expression, cellular DNA replication, cell cycle progression, differentiation and development is controlled. The question of "how" these features are controlled, however, is irrelevant. Persons of ordinary skill would have no difficulty in determining whether plant growth, gene expression, cellular DNA replication, cell cycle progression, differentiation and development were controlled by carrying out the claimed method. Accordingly, the claims are definite within the meaning of §112. *In re Mercier*, 185

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U.S.P.Q. 774 (C.C.P.A. 1975) (claims sufficiently define an invention so long as one skilled in the art can determine what subject matter is or is not within the scope of the claims).

The Office Action also asserts that the phrase "increasing or decreasing" E2F-dimerization partner (DP) protein activity in claim 1 is unclear. The phrase, however, is as clear as can be. One skilled in the art would be able to determine whether it "increases" or whether it "decreases."

The Office action also asserts that claim 1 is unclear in what specific type of activity is increased or decreased. The phrase "E2F activity" has been defined as "E2F binding to E2F binding sites in plant DNA."

The phrase "capable of" and "ability to" has been deleted from claim 1.

The phrase "interacting with" in claim 1 has been amended to recite "dimerizes with."

The term "alter" in claim 1 has been amended to "modulate" based on, for example, line 28, page 10 of the specification.

#### *B. Claim 4*

The subject matter of claim 4 has been introduced into claim 1. The term "modulated" does not appear in claim 1.

#### *C. Claim 5*

Claim 5 has been amended such that it refers to the steps outlined in amended claim 1.

The Office Action asserts that the phrase "the plant DP protein level" lacks antecedent support. A plant's "DP protein level", however, is an inherent feature of the plant and, thus, no antecedent basis is explicitly required.

Antecedent basis for the term "the E2F-DP DNA binding activity" is now present due to amendments to claim 1.

The term "altering" has been amended where appropriate. The phrase "alteration of the DP protein level" however, does not lack clarity. Alteration in the level of a protein can only be in the sense of increasing or decreasing.

The phrase "altering transactivation properties" has been amended to "altering E2F-DP transactivation properties," thus clarifying to which protein's properties are being referred.

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The phrase "transactivation properties" is not indefinite. The Office Action provides no evidence that one skilled in the art would not be able to determine whether a particular activity is a "transactivation property." The fact that there may be more than one property does not render the claim indefinite.

*D. Claim 6*

Regarding claim 6, the term "may" has been amended to recite "is."

Claim 6 has been amended to make it clear that the modification relates to an increase or decrease in DP protein activity. In addition, the phrase "modification of the levels or activity of plant E2F and/or plant Rb" is broadly drafted to include any modification of the levels or activity of plant E2F or plant Rb. The term is broad but not unclear.

The term "modified" has been amended to recite "increased or decreased."

*E. Claim 12*

The phrase "for expression of", "ability to", and "effect thereof" have been removed for the purposes of clarity.

The phrase "capable of altering" has been amended to recite "that increases or decreases."

*F. Claim 22*

Claim 22 has been amended to recite "a nucleic acid having a DP protein or peptide encoding sequence together with a sequence encoding an E2F protein or peptide."

The phrase "capable of", "ability to", and "effect thereof" have been removed for the purposes of clarity.

The term "altering" has been amended to read "increasing or decreasing."

The phrase "modulate E2F binding" encompasses, for example, both "enhancing the binding" and "diminishing the binding." The invention provides a method which increases or decreases DP activity – which includes modulating E2F binding to E2F binding sites and binding of DP to E2F (see, page 10, lines 7 to 10). Whilst the term may be broader than, for example "to enhance" it is not unclear.

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The Office Action asserts that the phrase "under the control of the same regulatory element or elements" is indefinite. Claim 23, however, has been amended to recite the regulatory element. One skilled in the art would be able to determine whether the sequences encoding the DP and E2F are under control of the same promoter or promoters.

*H. Claim 47*

The phrase "is capable of altering" in claim 47 has been amended to recite "increases or decreases."

The phrase "ability to dimerize" has been amended to "dimerization."

The phrase "ability to modulate" has been amended to "modulation of."

The phrase "effect thereof" has been removed.

Recitation of "altering" and "modulate" is clear and definite for the reasons presented above.

In view of the foregoing, the claims are clear and definite. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §112, second paragraph be withdrawn.

**IV. The Claimed Invention Is Supported by Ample Written Description**

Claims 1-6, 12, 13, 15, 22-24, and 47 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants traverse the rejection and respectfully request reconsideration because the specification provides ample written description supporting the claimed inventions.

The Office Action asserts that the specification does not describe other DNA sequences such as functional fragments or variants of SEQ ID NO:2, and also does not describe a representative number of species.

As stated in the "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1 'Written Description' Requirement":

Possession may be shown by actual reduction to practice, by a clear depiction of the invention in detailed drawings which permit a person

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skilled in the art to clearly recognize that applicant had possession of the claimed invention, or by a written description of the invention describing sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention.

In accordance with these standards, Applicants have indeed, provided a sufficient written description of the claimed inventions. Indeed, the claims have been amended to recite that the protein or peptide comprises one or more of the following structural features: a) the DNA binding domain, b) the heterodimerization domain, and c) the nuclear localization signal. These structural features are common to DP proteins, as outlined in figure 2, and as described on page 12, lines 3-7, and as such are a "recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus." Thus, claims recite a proper combination of structure and function.

In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph, as allegedly failing to provide sufficient written description be withdrawn.

#### **V. The Claimed Invention Is Sufficiently Enabled**

Claims 1-6, 12-14, 15-24, and 47 are rejected under 35 U.S.C. §112, first paragraph as allegedly failing to provide an enabling disclosure. The Office Action mistakenly asserts that the claimed invention "is not enabled because the function of a sequence cannot reliably be predicted on the basis of its structure or on the basis of its homology to other known sequences." The Office Action also appears to mandate a declaration regarding the availability of the deposit for pCLON33. Applicants traverse the rejection and respectfully request reconsideration because one skilled in the art would be able to practice the claimed invention without being required to perform undue experimentation.

##### **A. Claim 14**

The Examiner asserts that the plasmid pCLON33 "is required to practice the claimed invention." The Examiner also asserts that it does not appear that the specification provides a

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repeatable method for obtaining the plasmid. Although Applicants' specification provides ample basis for obtaining plasmid pCLON33, nonetheless, plasmid pCLON33 has been deposited under the Budapest Treaty as described on page 12 lines 26 *et seq.* of the specification. In addition, there is no reasonable basis for demanding an additional affidavit or declaration regarding the deposit of pCLON33 under the Budapest Treaty. The Examiner is requested to call Applicants' undersigned representative if there are any questions regarding this matter.

**B. Claims 1-6, 12, 13, 15-24, and 47**

As a preliminary matter, the Examiner mistakenly asserts that the "specification does not disclose specific functions for SEQ ID NOS: 1 [DNA sequence encoding wheat DP protein] or 2 [amino acid sequence of wheat DP protein], or their effect on plant cells or plants when expressed therein" (see, Office Action at page 7). Applicants' specification, however, teaches many specific uses for such sequences (see, for example, page 4, line 22 to page 5, line 10, and page 10, lines 19-23 of the specification).

The Office Action asserts that "the claimed invention is not enabled because the function of a sequence cannot reliably be predicted on the basis of its structure or on the basis of its homology to other known sequences" (see, page 8 of the Office Action). The Examiner cites Whisstock et al., Q. Rev. Biophys., 2003, 36, 307-340, which purportedly supports the Examiner's position. Thus, the Office Action appears to suggest that the functions ascribed to the DP protein recited in the claims are only based upon homology to other known sequences. Applicants disagree.

The claims have been amended, as described above, to recite that the proteins or peptides of the invention comprise at least one of the structural features a), b) and c) as described above. The specification teaches the function of these domains (see, for example, page 19, line 22 to page 21, line 16) and they are demonstrated to be present in other DP proteins, as shown in Figure 3. Construction of DNA sequences is facile to the extent that it can be carried out by machine routinely. The cloning and expression of these sequences is no more than the routine day to day task of one of ordinary skill in molecular biology armed with those resources now routinely available, and cannot be considered an undue burden in this context, especially since

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structural features are provided to guide the ordinarily skilled artisan in the selection of appropriate sequences. Indeed, the worker of ordinary skill in the art is not required by the patent specification to make ALL the possible permutations and combinations of DNA sequences encompassed by a claim, before deciding on the one to use. Thus, the function of the sequences may be deduced on the basis of, for example, sequence similarity coupled with the presence of the structural features now recited in the claim. Furthermore, the specification teaches methods of verifying the activity of the proteins (see, for example, those of Examples 2, 4, 6, and 7). Therefore, there is no amount of experimentation identified in the Office Action that would be undue in order to practice the claimed invention.

The Office Action also asserts that the invention is not enabled because "the effect of expressing in a cell a DP protein, alone or in combination with an E2F protein, is unpredictable, since different members of both the DP protein family and the E2F protein family vary with respect to their specific functions, and with respect to how they function when expressed independently and when coexpressed" (see, page 10 of the Office Action). The Office Action cites six references which purportedly supports the Examiner's position, only two of which relate to plant DP proteins. Applicants disagree.

The fact that DP proteins may have many different functions, particularly in non-plant cells, is wholly irrelevant in determining whether one skilled in the art can practice the claimed invention in plant cells without being required to perform undue experimentation. The various functions of DP proteins reported in the Hiebert, Dynlacht, Sawado, and Wu references are directed to non-plant cells. Whether or not these functions are "predictable" is irrelevant when determining whether undue experimentation is required to carry out the claimed method in plant cells.

Magyar et al., FEBS Lett., 2000, 486, 79-87 (hereinafter, the "Magyar reference) does not teach or suggest that Applicants' claimed invention does not work or would require undue experimentation to work. Rather, as acknowledged in the Office Action, the Magyar reference merely reports that *Arabidopsis thaliana* DP proteins do not group with animal DP families. Applicants are unable to understand any significance or relationship this plays in regard to Applicants' claimed invention. Again, nowhere does the Magyar reference teach or suggest that,

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because of the differences between *Arabidopsis thaliana* DP proteins and animal DP proteins, Applicants' claimed invention (which makes use of wheat DP proteins) would not function in plants, or would require undue experimentation to work in plants.

Mariconti et al., J. Biol. Chem., 2002, 277, 9911-9919 (hereinafter, the "Mariconti reference) also does not teach or suggest that Applicants' claimed invention does not work or would require undue experimentation to work. Rather, the Mariconti reference reports the existence of another group of E2F proteins in *Arabidopsis thaliana* which appear to lack the ability to bind to DP proteins, in addition to the group of E2F proteins that can bind to DP proteins. The Mariconti reference speculates that this additional group of E2F proteins can compete with the "wild-type" E2F proteins. Again, Applicants are unable to understand any significance or relationship this plays in regard to Applicants' claimed invention. Nowhere does the Mariconti reference teach or suggest that, because of the existence of another group of E2F proteins in *Arabidopsis thaliana*, Applicants' claimed invention (which makes use of wheat DP proteins) would not function in plants, or would require undue experimentation to work in plants. The Mariconti reference does not teach or suggest that Applicants' claimed methods would not work in plant cells that also express such additional group of E2F proteins.

The Office Action also asserts that the invention is not enabled because "the conditions for using a sequence as a probe are unpredictable, since the conditions under which a DNA probe will hybridize to a target sequence vary and depend in part on the specific sequence of the probe and target" (see, page 13 of the Office Action). The Office Action cites Gillespie, Vet. Microbiol., 1990, 24, 217-233 (hereinafter, the "Gillespie reference"), which purportedly supports the Examiner's position. Applicants again disagree.

As set forth in the Office Action, the Gillespie reference reports that specific hybridization between a DNA probe and its target sequence are affected by: 1) the concentration of probe and target molecules, 2) the length and sequence of the probe, 3) the hybridization temperature, and 4) the concentration of the salt and detergent present during hybridization. The fact that hybridization of a DNA probe to a target molecule is "affected" by any or all of these factors is wholly unsurprising. Indeed, these factors are simply the laws of physics that apply to hybridization of one entity to another entity. These factors, however, in no way, shape, or form

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amount to undue experimentation. Indeed, the use of DNA probes was routine in the art at the time of the Gillespie reference (1990), let alone as of 1999 (Applicants' earliest priority date). The literature is replete with references describing the use of DNA probes to nucleic acid molecules. Indeed, the general principles involved in the selection of DNA sequences for use as probes is part of the common general knowledge of the ordinarily skilled molecular biologist. Further, it is routine practice in the art to optimize detection by varying temperature and salt concentration until satisfactory detection is achieved, and/or, if necessary, to use a selection of probes derived from the sequence. Since the sequence of SEQ NO:1, from which the probe sequence must be derived, is defined, the selection of probes does not involve examination of a myriad of possibilities, but is limited by the sequence from which the probe is derived (SEQ ID NO:1) and the selection of those areas of the sequence with the appropriate physical properties for use as a probe. These properties are well known in the art, consequently this does not represent an undue burden but is simply routine practice in the art to which the application relates.

The Office Action also asserts that the invention is not enabled because "methods for inhibiting the expression of endogenous genes using antisense technology are unpredictable, since the ability of an antisense DNA sequence to inhibit gene expression is dependent on the specific structure of the DNA sequence and its target" (see, page 14 of the Office Action). The Office Action cites three references which purportedly supports the Examiner's position. Applicants again disagree.

None of the references cited in the Office Action teach or suggest that any amount of undue experimentation must be performed to practice the claimed invention. Rather, according to the Office Action, the three references report that some antisense compounds are better than others and that a high degree of sequence homology (i.e., greater than 75%) between the endogenous gene and the antisense compound is required in order for the antisense compound to be effective. The fact that some antisense compounds work better than others is not surprising, let alone sufficient to establish that undue experimentation is required to practice Applicants' claimed invention. In addition, the fact that a high degree of complementarity is also involved is also wholly unsurprising. It does not take any amount of undue experimentation to design an

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antisense compound with a sufficient degree of complementarity so as to effectuate hybridization. The general principals of the construction of antisense sequences and how to express them in plants is broadly appreciated in the art. Further reference is made to U.S. Patent No. 5,107,065 (cited in the current application and included therein by reference – see page 15, lines 20-27 of the specification) which teaches general principals of the construction of antisense compounds. These are reduced to practice by simple matching to the disclosed sequence. There is no undue burden on the ordinarily skilled artisan given the level of skill in this area and the availability of modern screening practices.

Thus, there is no reason to believe that one skilled in the art would be required to perform any amount of undue experimentation to make and use the claimed invention. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph be withdrawn.

**VL Conclusion**

In view of the foregoing, Applicants respectfully submit that the claims are in condition for allowance. An early notice of the same is earnestly solicited. The Examiner is invited to contact Applicants' undersigned representative at (215) 665-6914 if there are any questions regarding Applicants' claimed invention.

Respectfully submitted,

  
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